II. REMARKS

Formal Matters

Claims 1-6, 23, 24, 28, and 31-44 are pending after entry of the amendments set forth herein.

Claims 1-6, 23, 24, 28, and 31-38 were examined and were rejected. Claims 7-22, 25-27, 29, and 30 were withdrawn from consideration.

Claims 28, and 33-38 are amended. The amendments to the claims were made solely in the interest of expediting prosecution, and are not to be construed as an acquiescence to any objection or rejection of any claim. Support for the amendments to claims 28 and 33-38 is found in the claims as originally filed, and throughout the specification, in particular at the following locations: claim 28: paragraphs 00215- and 00216; and claims 33-38: paragraphs 00126, 00199, 00200, 00205, 00214, 00224, and 00228. Accordingly, no new matter is added by these amendments.

Claims 7-22, 25-27, 29, and 30 are canceled without prejudice to renewal, without intent to acquiesce to any rejection, and without intent to surrender any subject matter encompassed by the canceled claims. Applicants expressly reserve the right to pursue any canceled subject matter in one or more continuation and/or divisional applications.

Claims 39-44 are added. Support for new claims 39-44 is found in the claims as originally filed, and throughout the specification, including the following exemplary locations: paragraphs 00129-00131; and paragraph 00134. Accordingly, no new matter is added by these new claims.

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Rejections withdrawn

Applicants note with gratitude that the following rejections, raised in the January 24, 2003 Office Action, have been withdrawn: 1) rejection of claim 1 under 35 U.S.C.§112, second paragraph; 2) and rejection of claims 1-6, 23, 24, 28, and 31 under 35 U.S.C.§102(b).

Rejection under 35 U.S.C.§112, first paragraph

Claims 1-6, 23, 24, and 31-38 were rejected under 35 U.S.C.§112, first paragraph, as allegedly failing to comply with the enablement requirement. Claim 28 was rejected under 35 U.S.C.§112, first paragraph, as allegedly failing to comply with the enablement requirement. Claims 1, 2, 23, 28, 31, and

32 were rejected under 35 U.S.C.§112, first paragraph, as allegedly failing to comply with the written description requirement.

Claims 1-6, 23, 24, and 31-38; enablement

The Office Action stated that the specification does not reasonably provide enablement for practicing the claimed method using agents other than SEQ ID NO:1, 3, or 4. Applicants respectfully traverse the rejection.

The law regarding enablement of inventions is clear: "[t]he test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation."[1]

To aid in determinations of enablement, courts have identified eight factors for consideration: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability or unpredictability of the art; and (h) the breadth of the claims.[2]

The instant specification discusses a method of inhibiting formation of neurofibrillary tangles in an individual (claims 1 and 23); a method of reducing the level of neurotoxic carboxyl-terminal truncated apoE in a neuronal cell (claim 31); and a method of reducing formation of neurotoxic carboxyl-terminal truncated apoE in a neuronal cell (claim 32). The methods generally involve use of an agent that reduces formation of a neurotoxic carboxyl-terminal truncated form of apoE in a neuron (claims 1 and 32) or use of an agent that inhibits an enzymatic activity of an enzyme that catalyzes the cleavage of apoE to generate carboxyl-terminal truncated apoE (claims 23 and 31). Specification, paragraphs 00129-00134; and paragraphs 00143-00144.

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[1] *United States v. Telectronics, Inc.*, 8 USPQ 2d 1217, 1233 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989). See also *Genentech, Inc. v. Novo Nordisk*, 42 USPQ 2d 1001 (Fed. Cir. 1997), *cert. denied*, 522 U.S. 963 (1997); *Scripps Clinic and Research Foundation v. Genentech, Inc.*, 18 USPQ 2d 1001 (Fed. Cir. 1991).

[2] *Ex Parte Forman.*, 230 USPQ 546, 547 (Bd.Pat.App & Interf. 1986); and, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The specification states that examples of suitable agents include agents that inhibit a chymotrypsin-like serine protease, and provides references for such inhibitors, and generic formulas for such inhibitors. Specification, paragraphs 00132-00133. The specification further provides specific examples of suitable inhibitors. Specification, paragraph 00134; and Example 3, paragraphs 00236 and 00237. Thus, the specification provides ample support for methods of reducing the level of neurotoxic carboxyl-terminal truncated apoE and for methods of reducing the formation of neurotoxic carboxyl-terminal truncated apoE.

The specification further provides ample description for how to determine whether a given agent reduces formation of neurotoxic carboxyl-terminal truncated apoE or inhibits an enzyme that catalyzes the cleavage of apoE, forming neurotoxic carboxyl-terminal truncated apoE. Specification, paragraphs 00104-00115; and 0094-00103.

Applicants respectfully submit that the specification and the amended claims, coupled with the information known in the art, would enable one of skill in the art to use the invention without undue experimentation. Relevant enablement factors are discussed in detail below.

(a) the quantity of experimentation necessary:

The courts have clearly taught that the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. For example, see MPEP §2164.01.[3]

As the court explained[4]:

> "[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed."

Practitioners in the chemical and molecular biology arts frequently engage in extensive modification of reaction conditions and complex and lengthy experimentation where many factors must be varied to succeed in performing an experiment or in producing a desired result. The Federal Circuit has found that such extensive experimentation is not undue in the molecular biology arts. For example,

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[3] See also *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 227 USPQ 428 (Fed. Cir. 1985).

the court concluded that extensive screening experiments, while being voluminous, were not undue in view of the art which routinely performs such long experiments.[5]

The claimed methods require use of an agent that reduces formation of a neurotoxic carboxyl-terminal truncated form of apoE in a neuron or that inhibits an enzymatic activity of an enzyme that catalyzes the cleavage of apoE to generate carboxyl-terminal truncated apoE. The only experiments, if any, that need be performed to enable the entire scope of the claim are those designed to determine whether a given agent reduces formation of a neurotoxic carboxyl-terminal truncated form of apoE in a neuron or that inhibits an enzymatic activity of an enzyme that catalyzes the cleavage of apoE to generate carboxyl-terminal truncated apoE. As noted above, whether a given agent reduces formation of a neurotoxic carboxyl-terminal truncated form of apoE in a neuron or that inhibits an enzymatic activity of an enzyme that catalyzes the cleavage of apoE to generate carboxyl-terminal truncated apoE is readily determined, given the guidance in the specification. Such determination is carried out using routine experimentation, typically employing nothing more than performing the same assay disclosed in the specification. Since these experiments are routine in nature, no undue experimentation is required. In other words, the only experimentation that may be required to enable the claimed invention are those experiments to determine the presence of a certain activity, and since this only requires a routine assay on compounds to determine their activity, no undue experimentation is necessary.

(b) the amount of direction or guidance presented

The specification provides ample guidance as to compounds that will function in the methods as claimed. The specification states that examples of suitable agents include agents that inhibit a chymotrypsin-like serine protease, and provides references for such inhibitors, and generic formulas for such inhibitors. Specification, paragraphs 00132-00133. The specification further provides specific examples of suitable inhibitors. Specification, paragraph 00134; and Example 3, paragraphs 00236 and 00237. Thus, the specification provides ample support for methods of reducing the level of neurotoxic carboxyl-terminal truncated apoE and for methods of reducing the formation of neurotoxic carboxyl-terminal truncated apoE.

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[4] *In re Wands* 8 USPQ 2d at 1404
[5] *Hybritech v. Monoclonal Antibodies, Inc.* 231 USPQ 81 (Fed. Cir. 1986)

The specification further provides ample description for how to determine whether a given agent reduces formation of neurotoxic carboxyl-terminal truncated apoE or inhibits an enzyme that catalyzes the cleavage of apoE, forming neurotoxic carboxyl-terminal truncated apoE. Specification, paragraphs 00104-00115; and 0094-00103.

(c) the presence or absence of working examples:

Compliance with the enablement requirement under Section 35 U.S.C. §112, first paragraph does not require or mandate that a specific example be disclosed. The specification need not contain a working example if the invention is otherwise disclosed in such a manner that one skilled in the art would be able to practice the invention without undue experimentation.[6] Furthermore, "Nothing more than objective enablement is required, and therefore it is irrelevant whether [a] teaching is provided through broad terminology or illustrative examples."[7]

Nevertheless, actual working examples are disclosed in the specification. The specification provides working examples of three different peptides that were active in inhibiting the chymotrypsin-like serine protease that cleaves apoE to generate neurotoxic carboxyl-terminal truncated apoE. Specification, Example 3, paragraphs 00236 and 00237.

(d) the relative skill of those in the art:

The relevant ordinarily skilled artisan is generally a skilled laboratory technician with experience in molecular biology and/or a scientist with the equivalent of a doctoral degree in molecular biology techniques. Furthermore, such artisans are required to keep abreast of the latest technology through continuing education and reading of scientific journal articles. As such, the skill level of those using the claimed methods is high.

(e) the predictability or unpredictability of the art

The Office Action does not address the predictability of the art. However, given the ample guidance in the specification, those skilled in the art would reasonably expect that, in addition to the agents identified in the working examples, other agents as disclosed will function in the methods as claimed. It is Applicants' position that the identification of further agents that will function in the

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[6] In re Borkowski, 164 USPQ at 645.
[7] *In re Robins* 166 USPQ 552 at 555 (CCPA 1970).

claimed methods is not unpredictable.

Even if the Office took the position that the art is unpredictable, the courts have clearly taught that even in unpredictable arts the specification does not have to disclose every species of a genus that would work and every species that would not work.

The court has very clearly explained[8]:

> "To require such a complete disclosure would apparently necessitate a patent application or applications with thousands of catalysts....More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed. A potential infringer could readily avoid literal infringement of such claims by merely finding another analogous catalyst complex which could be used …."

(f) the breadth of the claims

The claims of the instant application encompass the use of agents that have the ability to effectively reduce formation of a neurotoxic carboxyl-terminal truncated form of apoE in a neuron or inhibit an enzymatic activity of an enzyme that catalyzes the cleavage of apoE to generate carboxyl-terminal truncated apoE. In other words, in order to fall within an instant claim, an agent must be able to reduce formation of a neurotoxic carboxyl-terminal truncated form of apoE in a neuron or inhibit an enzymatic activity of an enzyme that catalyzes the cleavage of apoE to generate carboxyl-terminal truncated apoE. *Thus, the claim language excludes use of agents that do not exhibit these activities.*

In summary, the amount of experimentation required to carry out the claimed methods would not be undue because a) working examples have been provided; b) guidance has been provided as to various agents that will function in the claimed methods; c) guidance has been provided as to how to determine whether a given agent will function in a claimed method; and d) one of skill in the art would be able to perform the experiments as a matter of routine to determine active agents.

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[8] *In re Angstadt*, 190 USPQ at 218.

The specification therefore provides sufficient enablement such that one of ordinary skill in the art would be able to practice the invention without undue experimentation.

The Office Action stated that the art recognizes that the term "agent" can pertain to chemical entities, pharmaceutical compositions, proteins, peptides, etc., and stated that for the claims which fail to recite limitations as to what constitutes an applicable agent, undue experimentation would be required to make and/or use the claimed invention.

However, as noted above, the claims require that an agent exhibit a particular activity, i.e., reduce formation of a neurotoxic carboxyl-terminal truncated form of apoE in a neuron or inhibit an enzymatic activity of an enzyme that catalyzes the cleavage of apoE to generate carboxyl-terminal truncated apoE. Thus, the claims exclude use of agents that do not exhibit such activities. It goes beyond the enablement requirement of 35 U.S.C.§112, first paragraph, to require a description of each and every agent that will function in the claimed methods.

The Office Action stated that Bi et al. ((July 17, 2001) *Proc. Natl. Acad. Sci. USA* 98:8832-8837; "Bi") teaches that the administration of protease inhibitors, specifically lysosomal inhibitors, can actually augment the formation of neurofibrillary tangles. The Office Action stated that it is possible for agents which may meet the limitations of the claims to have other undesirable effects, such as augmenting NFT formation or apoE degradation by other enzymes, creating other toxic apoE fragments. However, the claims recite "administering an agent that **reduces formation of** a neurotoxic carboxyl-terminal truncated form of apoE in a neuron." Any agent that does not reduce formation of a neurotoxic carboxyl-terminal truncated form of apoE in a neuron is excluded from the claim.

The Office Action stated that Ljundberg et al. ((2002) *Mol. Neurosci.* 13:867-870; "Ljundberg") teaches that expression of apoE4(Δ272-299) does not form neurofibrillary tangles but ring-like structures. However, upon careful reading of Ljundberg, Ljundberg in fact states their observations confirm the finding that carboxyl-terminal truncated apoE induces tangle-like structures in neurons. Ljundberg, page 867; page 868, column 2, second paragraph under "Results"; and Figure 1. Accordingly, Ljundberg does not support the enablement rejection.

Furthermore, Harris et al. ((Sept. 16, 2003; e-pub Aug. 25, 2003) *Proc. Natl. Acad. Sci. USA* 100:10966-10971; "Harris"), a copy of which is provided herewith as Exhibit 1, discusses the effects of apoE4(Δ272-299) in transgenic mice expressing apoE4(Δ272-299). Harris demonstrates that transgenic mice expressing apoE4(Δ272-299) in the brain died at 2-4 months of age; that cells in the cortex and hippocampus of these mice displayed Alzheimer's disease (AD)-like neurodegenerative alterations, including structures resembling neurofibrillary tangles characteristic of AD; and that mice expressing apoE4(Δ272-299) showed impaired learning and memory at 6-7 months of age. Thus, in view of Harris, and in view of the ample support in the specification, those of ordinary skill in the art would not need to conduct undue experimentation in order to practice the claimed methods.

Claim 28; enablement

The Office Action stated that the specification fails to provide any guidance for the successful treatment of Alzheimer's disease, and concluded that one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. Applicants respectfully traverse the rejection.

As discussed above instant specification teaches several agents that will reduce the formation of neurotoxic carboxyl-terminal truncated apoE in a neuronal cell. Also as discussed above, the instant specification provides working examples of three specific peptides, e.g., Ala-Ala-Pro-Phe (SEQ ID NO:1), Ala-Ala-Pro-Leu (SEQ ID NO:3), and Ala-Ala-Ala-Ala-Pro-Phe (SEQ ID NO:4) inhibit a chymotrypsin-like protease and reduce the level of neurotoxic carboxyl-terminal truncated apoE in a neuronal cell. The specification also teaches how to determine whether a given agent is efficacious in reducing the level of neurotoxic carboxyl-terminal truncated apoE in a neuronal cell. Furthermore, as discussed above, Harris (Exhibit 1) provides additional support for the fact that production of carboxyl-terminal truncated apoE in neuronal cells of mice produces symptoms of Alzheimer's disease (AD). Thus, those skilled in the art would have no reason to doubt that the specification is enabled for a method of treating AD, comprising administering an inhibitor of a chymotrypsin-like serine protease.

The Office Action cited Bi, and stated that since the claims are so broadly written, it is possible for agents that may meet the limitations of the claims to have other undesirable effects. However, claim 28 requires that the enzyme that catalyzes formation of neurotoxic carboxyl-terminal truncated apoE is

inhibited and the level of neurofibrillary tangles in a neuronal cell in the individual is reduced. Use of any agent that does not have the recited effects is excluded from the claim.

The Office Action cited Ljundberg, and stated that Ljundberg teaches that expression of apoE4(Δ272-299) does not form neurofibrillary tangles but ring-like structures. However, upon careful reading of Ljundberg, Ljundberg in fact states their observations confirm the finding that carboxyl-terminal truncated apoE induces tangle-like structures in neurons. Ljundberg, page 867; page 868, column 2, second paragraph under "Results"; and Figure 1. Accordingly, Ljundberg does not support the enablement rejection. Furthermore, as noted above, Harris provides further evidence for the fact that apoE4(Δ272-299) is neurotoxic and induces symptoms of AD in an animal model.

Claims 1, 2, 23, 28, 31, and 32; written description

The Office Action stated that the specification does not provide adequate written description of agents other than SEQ ID NO:1, 3, and 4.

However, the specification states that examples of suitable agents include agents that inhibit a chymotrypsin-like serine protease, and provides references for such inhibitors, and generic formulas for such inhibitors. Specification, paragraphs 00132-00133. The specification further provides specific examples of suitable inhibitors. Specification, paragraph 00134; and Example 3, paragraphs 00236 and 00237.

Applicants submit that the specification, by describing various agents that inhibit formation of neurotoxic carboxyl-terminal truncated apoE, and by providing **at least three** working examples of agents that inhibit formation of neurotoxic carboxyl-terminal truncated apoE, is in compliance with the written description requirement of 35 U.S.C.§112, first paragraph.

Applicants submit that the rejection of claims 1, 2, 23, 28, 31, and 32 under 35 U.S.C. §112, first paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejection under 35 U.S.C.§112, second paragraph

Claims 33-38 were rejected under 35 U.S.C.§112, second paragraph, as allegedly indefinite.

The Office Action stated that the term "kD" is a relative term that renders the claim indefinite. Applicants respectfully traverse the rejection.

Those of ordinary skill in the art understand the meaning of the term "kD." The term "kD" appears in numerous issued (and thus presumably valid) U.S. patents. See, e.g., U.S. Patent Nos. 6,630,148, 6,620,790, 6,544,519, 6,541,609, and 6,486,131. Accordingly, the term "kD" is clear, and the claims need not be amended.

Nevertheless, and without conceding as to the correctness of this rejection, claims 33-38 are amended to recite "as determined by sodium dodecyl sulfate polyacrylamide gel electrophoresis analysis."

Applicants submit that the rejection of claims 33-38 under 35 U.S.C. §112, second paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

III. CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number UCAL217.

Respectfully submitted,
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Date: Dec. 3, 2003

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